

### **REMARKS**

This response is due on February 5, 2004. No fees are believed to be due; however, should any fees be properly due in connection with the filing of this document, or should the extension of time fee be inadvertently omitted, the Commissioner is hereby authorized to deduct any such fees from Marshall, Gerstein & Borun, LLP account number 13-2855.

#### **The Outstanding Rejections**

The examiner rejected claims 1, 13, and 20 under the judicially-created doctrine of obviousness-type double patenting over claims 1, 9, and 32 of US Patent 6,537,755 (hereinafter "the '755 patent").

Claims 1 through 35 were also rejected under 35 USC §103(a) for being directed to subject matter assertedly rendered obvious by the disclosure of the '755 patent.

#### **Patentability Arguments**

##### **1. The Double Patenting Rejection**

The examiner rejected claims 1, 13, and 20 under the judicially-created doctrine of obviousness-type double patenting over claims 1, 9, and 32 of the '755 patent asserting that the '755 patent discloses methods involving detecting and identifying sequences in a target nucleic acid comprising contacting the target with one or mixtures of a plurality of probes. The applicants respectfully disagree.

MPEP §804 sets forth the basis for an obviousness-type double patenting rejection stating, "In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? If the answer is yes, then

an "obviousness-type" nonstatutory double patenting rejection may be appropriate." Section 804 further states, "When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." Thus the §103(a) analysis for obviousness is carried out with respect to the subject matter *defined only by the claims*, and reference to the specification is made only to more clearly define terms in a claim, or to identify only those portions of the specification that support the claimed subject matter to determine if a patent claim defines an obvious variant of an application claim.

Here, the subject matter of the rejected claims is not an obvious variation of the invention defined by the '755 patent claims because the method of the rejected claims represents a radical departure from previously known sequencing by hybridization (SBH) methods that cannot be deduced from the language of the cited patent claims with or without reference to the specification in the '755 patent. A comparison of the present method and that defined in the '755 patent makes the differences evident.

The method in claim 1 of the '755 patent is defined as follows.

1. A method of detecting a sequence of a target nucleic acid,  
comprising:

(a) contacting a target nucleic acid with one or more mixtures of a plurality of oligonucleotide probe molecules of predetermined length and predetermined sequence, wherein each probe molecule comprises an information region and at least two probe molecules have different information regions, under conditions which produce, on average, more probe:target hybridization with probe molecules which are perfectly complementary to the target nucleic acid in the information region of the probe molecules than with probe molecules which are mismatched in the information region, wherein the target nucleic acid is not attached to a support, and wherein the probe molecules are not attached to a support;

(b) detecting probe molecules that hybridize with the target nucleic acid, using a reader capable of detecting a single probe molecule that hybridizes to target nucleic acid; and

(c) detecting a sequence of the target nucleic acid by overlapping sequences of the information regions of at least two of the probe molecules contacted with the target in step (a).

In this solution-based method (see, *e.g.*, step (a) reciting that the target nucleic acid is not attached to a support, and the probe molecules are not attached to a support), probes that hybridize to a target nucleic acid are identified (step b) and a sequence in the target detected by overlapping sequences from at least two probes that hybridize to the target (step (c)). Even though the target is first contacted with "one or more mixtures of a plurality of oligonucleotide probe molecules" (step (a)), only those probes that hybridize are detected (step (b)) and provide information that is used to deduce sequences in the target.

Claim 1 in the present application, however, reads as follows.

1. A method of identifying one or more sequences of a target nucleic acid comprising:

a. contacting a target nucleic acid with a first set of pools of probes, wherein at least one pool in the set comprises a mixture of two or more probes having different sequences in information regions of the probes, under conditions which produce, on average, more probe:target hybridization with probes which are perfectly complementary to the target nucleic acid in the information region of the probes than with probes which are mismatched in the information regions;

b. detecting a first subset of pools for which a level of hybridization indicates that there is at least one perfectly complementary probe within each pool; and

c. identifying one or more sequences of the target nucleic acid from the first subset of pools detected in step (b) by compiling overlapping sequences of the information regions of the probes in the subset of detected pools, wherein one or more pooling false positive probes are eliminated as a result of compilation of overlapping sequences.

In this method, which may be performed in solution or may utilize target and/or probes attached to a support, the target is contacted with "a set of pools of probes" (step (a)), and a subset of *pools* is detected wherein at least one probe in a pool hybridizes to the target (step (b)). The specific probe(s) in the pool that hybridizes to the target is not individually identified, but instead, each probe in the detected *pool* is "assumed" to be one that hybridizes to the target, and as a result, every sequence of every probe in the entire pool is used to deduce a sequence in the target. This assumption introduces a large number of false positive hybridizations, for example, in those instances wherein only one probe in the pool actually hybridizes to the target, but sequences from all probes in the pool are used in an overlapping sequence algorithm to determine target nucleic acid sequences. The false positive hybridizations artificially introduced in this method are eliminated during the overlapping sequence analysis (step(c)) by virtue of the fact that, while some false positive probe sequences may overlap with other false positive probe sequences, the sequence(s) deduced from these overlapping regions will eventually "die out" (*i.e.*, quit growing in length) because they are, in fact, random and unrelated to the target sequence. Only overlapping probes that actually hybridize to the target (*i.e.*, the "true positives") will permit deduction of a sequence of increasing length that is not random and which corresponds to sequences in the target nucleic acid.

Even though the two methods employ mixtures of probes, the two methods differ because in the method of the rejected claim, (i) no single probe that specifically hybridizes to the target need be identified in the detected "positive" pool from step (b), and (ii) sequences from all probes in any "positive" pool are included in the overlapping sequence algorithm, thereby intentionally introducing a significant number of false positives. In contrast, the method of the '755 patent requires identification of individual and specific probes that

actually hybridize to the target and false positives are introduced only if they are misconstrued to hybridize to the target. As a result, only sequences from probes known or believed to hybridize to the target are used in the subsequent data analysis. The two methods are therefore performed in completely different ways, provide completely different sets of experimental data, and require completely different methods of data analysis.

Because the two methods are so unrelated, the applicants submit that the method of the rejected claims could not be deduced from a reading of the '755 claims alone, with or without reference to the specification. Accordingly, the applicants submit that the rejection of claims under the judicially-created doctrine of obviousness-type double patenting is improper and must be withdrawn.

## **2. The §103 Rejection**

Claims 1 through 35 were also rejected under 35 USC §103(a) for being directed to subject matter assertedly rendered obvious by the disclosure of the '755 patent. In the discussion above, the applicants show that the method recited in the present claims is not an obvious variant of the method recited in the '755 patent claims, thereby establishing the impropriety of the double patenting rejection which requires comparison of claim language only, *i.e.*, the disclosure in the cited patent specification is excluded from the analysis. Even if the disclosure of the '755 patent specification is added to the prior art as in this rejection under §103, however, the applicants submit that presently claimed invention is still unobvious because nothing in the '755 patent discloses (i) carrying out the method in the manner presently claimed, (ii) providing the experimental data that is obtained in the presently claimed method, or (iii) methods for analyzing experimental data that include the

intentional inclusion of a large number of false positive sequences. For this reason alone the rejection is improper and must be withdrawn.

More importantly, however, the applicants submit that the '755 patent does not qualify as prior art to the present invention because the subject matter of the '755 claims and the presently rejected claims were commonly owned by Callida, or under obligation to be assigned to this common owner, at the time the subject matter of the rejected claims was made.

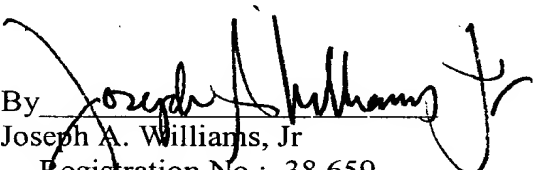
Accordingly, the applicants submit that the rejection under 35 USC §103(a) may properly be withdrawn.

#### **SUMMARY**

In view of the amendments and remarks presented herein, the Applicants request withdrawal of the rejections and favorable reconsideration of the claims.

Dated: March 9, 2004

Respectfully submitted,

By   
Joseph A. Williams, Jr.  
Registration No.: 38,659  
MARSHALL, GERSTEIN & BORUN LLP  
233 S. Wacker Drive, Suite 6300  
Sears Tower  
Chicago, Illinois 60606-6357  
(312) 474-6300  
Attorney for Applicant